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**(54)PRODUCTION OF COLLAGEN FIBER
NONWOVEN FABRIC SHEET**

(57)Abstract:

PURPOSE: To obtain a collagen fiber nonwoven fabric sheet sufficiently exhibiting hemostatic ability as a hemostatic agent, improved in operability in treating hemostasis and capable of rapidly and effectively applying to every wounds in a surgery region.

CONSTITUTION: This producing method comprises

discharging an acidic solution of a soluble collagen from a spinneret into an aqueous solution of concentrated salts to solidify the collagen, cutting the resultant regenerated collagen fiber and dispersing the collagen fiber into an organic solvent not dissolving collagen or a mixed solution of the organic solvent with water and making the dispersion into a nonwoven sheet.

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(54)【発明の名称】 コラーゲン繊維不織シートの製造方法

(57)【要約】

【目的】 止血材としての止血能を十分発揮し、かつ止血処置時の操作性を向上させ、外科領域におけるあらゆる創傷部に対して迅速で有効に適応できるコラーゲン繊維不織シートを得る、またこれを安全に得る。

【構成】 可溶化コラーゲンの酸性溶液を紡糸口金より濃厚塩類水溶液中に吐出させて凝固、再生したコラーゲン繊維を切断し、コラーゲンを溶解しない有機溶剤または有機溶剤と水との混合溶液で分散、抄造する。

【特許請求の範囲】

【請求項1】 可溶化コラーゲンの酸性溶液を紡糸口金より濃厚塩類水溶液中に吐出させて凝固、再生したコラーゲン繊維を切断し、コラーゲンを溶解しない有機溶剤または有機溶剤と水との混合溶液で分散、抄造することを特徴とするコラーゲン繊維不織シートの製造方法。

【請求項2】 抄造の際または抄造した後、生体吸収性繊維を混合または積層して複合する請求項1記載のコラーゲン繊維不織シートの製造方法。

【発明の詳細な説明】

【0001】

【産業上の利用分野】本発明は、外科領域における創傷部に迅速、かつ有効に適応できる止血材として有用なコラーゲン繊維不織シートの製造方法に関する。

【0002】

【従来の技術】近年、各医療施設で大手術が比較的頻繁に行われるようになったが、手術中の患者の出血をいかに予防し、また止血を確実に、かつ短時間に行うかが手術後の経過を左右する重要な因子となっている。例えば、外科手術時の止血法としては、圧迫法、結紮法、電気凝固法やトロンビンやフィブリン糊法等の生理活性物質の応用等がある。出血点のはっきりしている動脈性出血に対しては、一般に結紮法や電気凝固法が用いられ、静脈性出血に対しては、圧迫だけでも充分であり、止血は容易である。

【0003】しかしながら、実質臓器からの出血や毛細管性出血に対しては、これらの止血法では効果のない場合があり、肝不全や心臓血管外科領域で出血傾向にある場合には、特に止血に困難をきたす。このような場合、出血面に接触させるだけで血液凝固反応を促進し、速やかに血栓を形成し出血を阻止する局所吸収止血材が、手術時間を短縮するのみならず、術後の再出血をも防止し、安全な術後管理にも貢献するので効果的である。

【0004】この目的で、近年、生体由来の蛋白質、すなわち、抗原性が低く生体に安全に吸収されるためアレルギー反応と異物反応を最小限に止め得る蛋白質であるコラーゲンをを用いた局所止血材が、それ自身の生理活性作用を有し、止血効果も高いこともあって盛んに臨床応用されるようになってきている。

【0005】現在、実用化されているコラーゲン製局所止血材には、天然のコラーゲン繊維を微粉碎してフレーク状にしたものやコラーゲン溶液を凍結乾燥し平板状のスポンジにしたものがあるが、前者については、フレーク状であるために血液に流され飛び散るため止血効果があまり期待できないし、静電気を帯びやすく使用の際に、手やピンセットに付着しやすいという操作面での難点がある。一方、後者については、平板状であることから複雑な形状の創傷面に対する密着性が十分でなく、圧迫止血もできなくなるので、前者と同様止血効果があまり期待できない。

【0006】かかる欠点を改善するものとして、コラーゲン繊維の集合体よりなる止血材が提案されている。コラーゲン繊維集合体は、コラーゲン溶液を高濃度の塩類溶液にて凝固、再生させて繊維とし、塩類を洗浄除去した後乾燥することにより得ることができる（人工臓器19巻3号（1990）P. 1235～1238、特開平4-61862号公報）。しかし、この方法で得られるコラーゲン繊維集合体は、繊維が不規則に絡み合った綿塊状であるため、使用する際には、創傷面形状に合わせて均一に止血材を当てるために再度加工する必要があるが、綿塊の繊維密度や厚さを手作業によって均一にすることは困難である。また、広範囲の創傷面に適応する際、複数の綿塊を並べ合わせて使用すると、綿塊間の絡みがなく綿塊間に割れが生じ易く、止血不良をきたす原因になる。

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【0007】不規則に絡み合った綿塊の大きさや繊維密度を一定にするためには、エアブロー等の開繊処理を行う（人工臓器22巻2号（1993）P. 348～352）等の特別な手段が必要であるが、異物の混入や製造コストの面から実施が困難である。

【0008】

【発明が解決しようとする課題】止血材をその操作性から評価した場合、展開綿体が最もよいことは、オキシセルロースでの臨床使用から明らかであることから、本発明の目的は、止血材としての止血能を十分発揮し、かつ止血処置時の操作性を向上させ、外科領域におけるあらゆる創傷部に対して迅速で有効に適応できるコラーゲン繊維不織シートを得ることにあり、本発明の他の目的は、かかるコラーゲン繊維不織シートを安全に得ることにある。

【0009】

【課題を解決するための手段】本発明は、可溶化コラーゲンの酸性溶液を紡糸口金より濃厚塩類水溶液中に吐出させて凝固、再生したコラーゲン繊維を切断し、コラーゲンを溶解しない有機溶剤または有機溶剤と水との混合溶液で分散、抄造することを特徴とするコラーゲン繊維不織シートの製造方法にある。

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【0010】本発明において用いる可溶化コラーゲンは、繊維状に再生可能なコラーゲンであれば特に限定されず、酸、アルカリ、酵素等によって可溶化したコラーゲンであるが、可溶化の際、コラーゲンの抗原性発現部位であるテロペプチドを除去し免疫毒性を低下させた、酵素処理またはアルカリ処理により可溶化したいわゆるアテロコラーゲンであることが好ましい。

【0011】可溶化コラーゲンよりコラーゲン繊維を得るに当たっては、可溶化コラーゲンを酸性水溶液に溶解し、このコラーゲン酸性溶液をギャポンプを用いて一定量づつ紡糸口金より紡糸浴の濃厚塩類水溶液中に吐出させ紡糸することによりコラーゲン繊維を得る。コラーゲン酸性溶液は、均一でできるだけ高濃度であることが紡

糸にはよいが、コラーゲン濃度が高すぎると粘度が高くなり使用し難くなるので、コラーゲン濃度は、用いるコラーゲンの分子量にもよるが、0.5～10wt%とすることが好ましい。また、酸性水溶液は、均一溶液を簡便に調製するためには、用いるコラーゲンの等電点にもよるが、pHが1.5～5.0の塩酸水溶液を用いることが好ましい。

【0012】コラーゲンは、溶液状態では熱変性し易いため、用いるコラーゲンの安定性にもよるが、コラーゲン酸性溶液の温度を0～35℃とすることが好ましい。紡糸浴に用いる濃厚塩類水溶液における塩類としては、コラーゲンの凝固性、安全性から、塩化ナトリウム、塩化カリウム、塩化アンモニウム、硫酸ナトリウム、硫酸カリウム及び硫酸アンモニウムが好ましく用いられ、水溶液の塩類濃度は、高速で安定した紡糸を行うためには、飽和濃度の60%以上の濃度とするのが好ましい。また、紡糸温度は、高温ではコラーゲンの熱変性が促進されるので、用いるコラーゲンの安定性にもよるが、10～40℃であることが好ましい。

【0013】紡糸浴で凝固、再生して得られたコラーゲン繊維は、不織シートとするために、短繊維に切断される。切断長は、短かすぎると、繊維間の絡まりが少なくなり止血の際進む血液に抗する強度を有する不織シートを得ることが困難となり、また不織シート取扱い時に短繊維が飛散し易く適応部位以外への汚染を招き、長すぎると、繊維間の絡まりが過度になり均一な分散液の調製及び均一な厚さの不織シートを得ることが困難となるので、好ましくは1～50mm、より好ましくは1～30mmとする。コラーゲン繊維の切断は、紡糸以降分散、抄造までのいずれの段階で行ってもよいが、紡糸して得られた繊維を洗浄した後に、はさみ、切断機等切断することが好ましく、特に切断方法には制限はないが、引きちぎったり、押圧するような切断方法は、避けるのがよい。

【0014】紡糸して得られたコラーゲン繊維は、高濃度の塩類を含有したゲル状の形態をしているので、紡糸後塩類及びその他コラーゲン以外の不純物を除去するため洗浄する。塩類等の除去に先立ち、架橋処理によってコラーゲン繊維を水不溶化した場合は、洗浄剤として塩類の洗浄効率の高い水を用い、洗浄する。また、架橋処理を行わない場合は、コラーゲン繊維は、水溶性であるのでアルコール類と水との混合液を用い、洗浄する。

【0015】アルコール類としては、イソプロパノールが好ましく用いられ、アルコール類の比率が高い程塩類の洗浄効率が低下するので、コラーゲン繊維を溶解しない範囲でかつ洗浄効率を低下させない範囲とする必要があり、アルコール類比率を30～90vol%とすることが好ましい。また、洗浄温度は、洗浄効率からはできるだけ高いほうがよいが、コラーゲンの熱変性を防止する上から、用いるコラーゲンの安定性にもよるが、10

～40℃とすることが好ましい。

【0016】切断されたコラーゲン繊維は、コラーゲンを溶解しない有機溶剤または有機溶剤と水との混合溶液に分散させ、分散液を抄造して不織シートとする。分散媒としては、コラーゲンを溶解せず、かつ分散性が良好であると共に除去し易いことが必要であり、アルコール類、ケトン類、エーテル類等の有機溶剤が用いられるが、なかでも溶剤の非残留性、安全性からエタノール、イソプロパノールが好ましく用いられる。また、通常抄造における分散液には、分散性を高める目的で粘度調整剤を添加するのが一般的であるが、医療材の製造目的には用いることができないため、水を添加して分散性を高めた（溶液粘度を高めると共に繊維の膨潤により絡みが防止される）有機溶剤と水との混合溶液も用いられる。

【0017】また、脱塩洗浄に用いた洗浄液と同じ組成の分散媒を用いることにより、製造の合理化を可能とする。分散液のコラーゲン繊維濃度は、低い程均一に分散し易く、抄造において均一な厚さと密度の不織シートが得られるが、あまり低いと、大量の分散液と大きな装置を必要とするため、0.01～1.00wt%とすることが好ましい。

【0018】コラーゲン分散液は、抄造装置における漉き網の下部から均等に抜液することにより、コラーゲン短繊維が漉き網上に順次沈積して均一なコラーゲン繊維不織シートが形成される。コラーゲン繊維不織シートの厚さは、任意に設定できるが、抄造を繰り返すかまたは不織シートを積層して厚みを調整したり、多層化することもできる。

【0019】また、本発明においては、抄造の際または抄造した後、キチン、キトサン、酸化セルロース、ポリ乳酸、ポリグリコール酸、異種コラーゲンの等の生体吸収性繊維を混合または積層して複合したコラーゲン繊維不織シートを得ることができる。生体吸収性繊維との複合は、抄造の際に、生体吸収性繊維をコラーゲン分散液に添加する或いは生体吸収性繊維の分散液を併用する等により生体吸収性繊維をコラーゲン不織シートに混合或いは積層するか、または抄造した後に、得られたコラーゲン繊維不織シートに生体吸収性繊維不織シートを積層して複合する。かかる生体吸収性繊維の複合により、抗菌性、薬物放出性等の機能を付与した、或いは低コストのコラーゲン繊維不織シートを得ることができる。

【0020】得られたコラーゲン繊維不織シートは、減圧乾燥等により乾燥され、さらに滅菌、または必要に応じ架橋処理する等止血材として必要な安全性、取扱い性を考慮した任意の仕上げが施される。

【0021】

【実施例】以下、本発明を実施例により具体的に説明する。なお、コラーゲン繊維不織シートの性能評価は、次に記す方法に拠った。

【0022】1) 止血性：実験開始前にヘパリン100

$\mu/k g$ を全身に投与した成犬を全身麻酔下に開腹し、脾臓の皮膜のみを $1\text{ cm} \times 1\text{ cm}$ の大きさにメスで剥離した箇所に、 0.1 g の止血材を30秒間圧迫した後の出血量を一定時間毎に観察した。

ランクA 1分以内に止血が完了

ランクB 3分以内に止血が完了

ランクC 5分以内に止血が完了

【0023】2) 均一性(目付けの変動): 均一から不均一までを5段階で評価判定し、均一性の高い方を5、低い方を1とした。

3) 創傷部接触性: 良好から劣るまでを5段階で評価判定し、良好の方を5、劣る方を1とした。

4) 単繊維間の接着: 無しから多いまでを5段階で評価判定し、無い方を5、多い方を1とした。

【0024】(実施例1) 新鮮牛皮より得られた不溶性コラーゲンを蛋白質分解酵素のペプシンにて処理してアテロコラーゲンを得た。このアテロコラーゲンを $\text{pH}2$ に調整した塩酸水溶液に溶解し、温度 25°C 、コラーゲン濃度 $5\text{ wt}\%$ の酸性溶液とした後、孔径 $100\mu\text{m}$ 、孔数200の紡糸口金より、温度 25°C の硫酸ナトリウム $20\text{ wt}\%$ 水溶液からなる紡糸浴中に吐出して、凝固、再生し、再生コラーゲン繊維をイソプロパノール80/水20(vol%)の混合液で温度 25°C で洗浄してコラーゲン繊維を得た。

【0025】得られたコラーゲン繊維を、切断し、表1に示すa~fの条件にて分散液を調製して、濾き網目20メッシュ、濾き網面積 300 cm^2 、抜液速度 $2.3\text{ ml}/5\text{ cm}^2$ の条件にて抄造した後、減圧乾燥し、コラーゲン繊維不織シートを得た。得られた各コラーゲン繊維不織シートの性能を表2に示した。得られた各コラーゲン繊維不織シートは、外観、風合い、強度等に若干差異はみられるものの、止血材として良好な物性を保持し、いずれも高い止血能を有するものであった。

【0026】(実施例2) 新鮮牛皮より得られた不溶性コラーゲンをペプシンにて処理してアテロコラーゲンを得た。このアテロコラーゲンを $\text{pH}2$ に調整した塩酸水溶液に溶解し、温度 25°C 、コラーゲン濃度 $5\text{ wt}\%$ の酸性溶液とした後、孔径 $100\mu\text{m}$ 、孔数200の紡糸口金より、温度 25°C の硫酸ナトリウム $20\text{ wt}\%$ 水溶液からなる紡糸浴中に吐出して、凝固、再生し、再生繊維をイソプロパノール80/水20(vol%)の混合液で温度 25°C で洗浄してコラーゲン繊維(イ)を得た。

【0027】一方、新鮮牛皮より得られた不溶性コラーゲンを硫酸ナトリウムと水酸化ナトリウムとモノメチルアミンの混合溶液にて処理してアテロコラーゲンを得た。このアテロコラーゲンを同様にして紡糸、洗浄してコラーゲン繊維(ロ)を得た。得られた2種のコラーゲン繊維を、表1に示すaの条件にて、切断し、分散液を調製して、抄造し、それぞれ不織シートとした後、減圧

乾燥し、積層して多層状のコラーゲン繊維複合不織シートを得た。得られたコラーゲン繊維複合不織シートの性能を表2に示したが、得られたコラーゲン繊維複合不織シートは、止血材として十分な性能を有するものであった。

【0028】(実施例3) 実施例2において、コラーゲン繊維(ロ)に代えてキトサン繊維を用いた以外は、実施例2と同様にしてコラーゲン繊維複合不織シートを得た。得られた複合不織シートの性能を表2に示した。

10 【0029】(実施例4) 実施例2において用いたコラーゲン繊維(イ)及びコラーゲン繊維(ロ)をそれぞれ 10 mm に切断し、イソプロパノール中に2種短繊維の混合比(wt比)1:1、繊維濃度 $0.1\text{ wt}\%$ に分散させて分散液を調製し、抄造した後、減圧乾燥し、混合状態のコラーゲン繊維複合不織シートを得た。得られたコラーゲン繊維複合不織シートの性能を表2に示したが、得られたコラーゲン繊維複合不織シートは、止血材として実用的に十分な性能を有するものであった。

20 【0030】(実施例5) 実施例4において、コラーゲン繊維(ロ)に代えてキトサン繊維を用いた以外は、実施例4と同様にしてコラーゲン繊維複合不織シートを得た。得られたコラーゲン繊維複合不織シートの性能を表2に示したが、得られたコラーゲン繊維複合不織シートは、止血材として実用的に十分な性能を有するものであった。

30 【0031】(比較例1) 実施例1において紡糸して得た再生コラーゲン繊維を、イソプロパノール/水の代わりにメタノールを用いて温度 25°C で洗浄し、減圧乾燥した後、長さ 10 mm に切断し、 $30\text{ ml}/\text{sec}$ の風速で10分のエアブローにより分散させ、コラーゲン繊維綿状体を得た。得られたコラーゲン繊維綿状体の性能を表2に示したが、得られたコラーゲン繊維綿状体は、均一性に欠けるため創傷部との密着には大量の綿状体が必要とした。また止血処置に際して綿状体では創傷部位に合わせる場合、ピンセットが使えず、手や指で必要量を分別せねばならず、安全性の面だけでなく、操作が煩雑となった。

40 【0032】(比較例2) 実施例1において得られたコラーゲン繊維を、 $\text{pH}4$ の希塩酸にグルタルアルデヒド $0.5\text{ wt}\%$ 、塩化ナトリウム $15\text{ wt}\%$ を添加した溶液に15分浸漬して架橋処理した後、水で十分に洗浄した。次いで長さ 10 mm に切断し、凍結乾燥してコラーゲン繊維綿状体を得た。得られたコラーゲン繊維綿状体の性能を表2に示したが、得られたコラーゲン繊維綿状体は、繊維が硬化しているため、柔軟性に欠け創傷部との接触性が劣り、また止血能も低下していた。

50 【0033】(比較例3) 比較例2においてグルタルアルデヒドで架橋処理して得られたコラーゲン繊維を、長さ 10 mm に切断し、繊維濃度 $0.1\text{ wt}\%$ に水に分散させ、抄造した後、減圧乾燥してコラーゲン繊維不織シ

ートを得た。得られたコラーゲン繊維不織シートの性能を表2に示したが、得られたコラーゲン繊維不織シートは、単繊維間の接着が大きく、粗硬なため、創傷部との接触性が劣り、また止血能も低下していた。

【0034】(比較例4)実施例1において得られたコラーゲン繊維を、長さ10mmに切断し、繊維濃度0.1wt%になるよう水に加えたところ、コラーゲン繊維は、水に溶解し、抄造することが不可能であった。

【0035】

* 【表1】

条件	繊維長 (mm)	分散媒 (vol%)	コラーゲン繊維 濃度(vt%)
a	10	IPA100	0.1
b	40	IPA100	0.1
c	10	IPA80/水20	0.1
d	0.5	IPA100	0.1
e	120	IPA100	0.1
f	10	IPA100	3.0

* IPA:イソプロパノール

【表2】

	形状	不織シート 厚さ(mm)	止血性 (ランク)	均一性	創傷部 接触性	単繊維間 の接着
実施例1 a	シート状	6	A	4~5	5	5
b	シート状	6	A	4	5	5
c	シート状	5	A	5	5	4
d	シート状	6	A~B	4	3	5
e	シート状	8	A~B	3	3	5
f	シート状	140	A~B	3	4	5
実施例2	シート状	5	A	5	5	5
" 3	シート状	5	A	4~5	5	5
" 4	シート状	5	A~B	5	5	5
" 5	シート状	5	A~B	4~5	5	5
比較例1	綿状	—	B	1	2	3
" 2	綿状	—	C	3	2	3
" 3	シート状	6	C	3	1	1
" 4	抄造不可	—	—	—	—	—

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**(54) PRODUCTION OF COLLAGEN FIBER
NONWOVEN FABRIC SHEET**

(57) Abstract:

PURPOSE: To obtain a collagen fiber nonwoven fabric sheet sufficiently exhibiting hemostatic ability as a hemostatic agent, improved in operability in treating hemostasis and capable of rapidly and effectively applying to every wounds in a surgery region.

CONSTITUTION: This producing method comprises discharging an acidic solution of a soluble collagen from a spinneret into an aqueous solution of concentrated salts to solidify the collagen, cutting the resultant regenerated

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DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[Industrial Application] this invention relates to the manufacture method of a collagenous-fiber nonwoven sheet useful as **** material which can be effectively [quickly and] adapted for the wound section in a surgery field.

[0002]

[Description of the Prior Art] Although a major company way came to be performed comparatively frequently in each medical facilities in recent years, bleeding of the patient under operation is prevented how, and it has become the important factor which influences the progress after whether it carries out for a short time certainly performing an operation on ****. For example, as a **** method at the time of a surgical operation, there is application of physiological active substances, such as the pressing method, the ligating method, an electric coagulation method, a thrombin, and a fibrin paste method, etc. generally to the artery nature bleeding to which the bleeding point has clarified, the ligating method and an electric coagulation method use -- having -- vein nature bleeding -- receiving -- pressure -- it comes out enough, and it is and **** is easy

[0003] However, especially in may be ineffective by these **** methods to the bleeding from real internal organs, or capillary tube nature bleeding and being in a bleeding inclination in hepatic insufficiency or a heart blood vessel surgery field, it causes difficulty to ****. In such a case, since the partial absorption **** material which promotes a blood coagulation reaction only by making a bleeding side contact, forms a thrombus promptly, and prevents bleeding also prevents postoperative re-bleeding and it not only shortens operation time, but contributes to safe postoperative management, it is effective.

[0004] For this purpose, since the protein of the living body origin, i.e., antigenicity, is absorbed to a living body safely [it is low and] in recent years, it has a physiological activity operation of itself, and since the **** effect is also high, clinical application of the partial **** material using the collagen which is the protein which can stop an allergic reaction and foreign body reaction to the minimum is carried out increasingly briskly.

[0005] Although there are some which freeze-dried the thing and the collagen solution which pulverized a natural collagenous fiber and made into the shape of flakes, and used as plate-like sponge in the partial **** material made from a collagen put in practical use now, in order it is passed by blood since it is flakes-like, and it scatters, a **** effect cannot seldom expect and the difficulty in respect of [of being easy adhering to a hand or a pincette] operation is in the case of use about the former that it is easy electrifying. On the other hand, the adhesion to the wound side of a configuration complicated from being plate-like about the latter is not enough, and since pressure **** also becomes impossible, the **** effect can seldom expect like the former.

[0006] As what improves this fault, the **** material which consists of the aggregate of a collagenous fiber is proposed. It can obtain by drying, after the collagenous-fiber aggregate's solidifying and reproducing a collagen solution in high-concentration saline, considering as fiber and carrying out

washing removal of the salts (artificial organ 19 volume 3 No. (1990) P.1235-1238, JP,4-61862,A). However, although it is necessary to process it again in order to apply **** material uniformly according to a wound side configuration in case the collagenous-fiber aggregate obtained by this method is used, since fiber is the cotton massive which became entangled irregularly, it is difficult the aggregate to make the fiber density and thickness of **** uniform by the handicraft. Moreover, if two or more **** are put in order and used in case it is adapted for a wide range wound side, there is no debt between ****, and it will be easy to produce a crack between ****, and will become the cause which causes poor ****.

[0007] Although special meanses, such as performing opening processing of an air blow etc. (artificial organ 22 volume 2 No. (1993) P.348-352), are required in order to make regularity the size and fiber density of **** which became entangled irregularly, mixing of a foreign matter or the field of a manufacturing cost to operation is difficult.

[0008]

[Problem(s) to be Solved by the Invention] When **** material is evaluated from the operability, that expansion **** is the best Since it is clear from the clinical use by the oxy-cellulose, the purpose of this invention Demonstrate ***** as **** material enough, and the operability at the time of **** disposal is raised. Being in obtaining the collagenous-fiber nonwoven sheet which can be effectively [quickly and] adapted to all the wound sections in a surgery field, other purposes of this invention are to obtain this collagenous-fiber nonwoven sheet safely.

[0009]

[Means for Solving the Problem] this invention cuts the collagenous fiber which was made to breathe out the acidic solution of a solubilization collagen in thick salts solution from a spinneret, and was solidified and reproduced, and is in the manufacture method of the collagenous-fiber nonwoven sheet characterized by distributing and milling paper by the mixed solution of the organic solvent or the organic solvent, and water which do not dissolve a collagen.

[0010] Although the solubilization collagen used in this invention is a collagen which it was not limited especially when it was a reproducible collagen fibrous, but was solubilized with an acid, alkali, the enzyme, etc., it is desirable in the case of solubilization that it is the so-called atelocollagen solubilized according to the enzyme processing or the alkali treatment to which the terrorism peptide which is the antigenicity manifestation part of a collagen was removed, and immunity toxicity was reduced.

[0011] In obtaining a collagenous fiber from a solubilization collagen, a solubilization collagen is dissolved in acid solution and a collagenous fiber is obtained by making this collagen acidic solution breathe out in the thick salts solution of a spinning bath, and carrying out spinning from a constant-rate [every] spinneret, using a gear pump. A collagen acidic solution is uniform, and since viscosity will become high and it will be hard coming to use it if collagen concentration is too high although it is good for spinning that it is high concentration as much as possible, although based also on the molecular weight of the collagen to be used, considering as 0.5 - 10wt% is desirable [collagen concentration]. Moreover, although acid solution is based also on the isoelectric point of the collagen to be used in order to prepare a uniform solution simple, it is desirable that pH uses the hydrochloric-acid solution of 1.5-5.0.

[0012] Since it is easy to carry out thermal denaturation of the collagen in the state of a solution, although it is based also on the stability of the collagen to be used, it is desirable to make temperature of a collagen acidic solution into 0-35 degrees C. As salts in the thick salts solution used for a spinning bath, a sodium chloride, potassium chloride, an ammonium chloride, a sodium sulfate, potassium sulfate, and an ammonium sulfate are preferably used from the freezing characteristic of a collagen, and safety, and in order to perform spinning stabilized at high speed, as for the salts concentration of solution, it is desirable to consider as 60% or more of concentration of saturated concentration. Moreover, since the thermal denaturation of a collagen is promoted, although spinning temperature is based also on the stability of the collagen to be used at an elevated temperature, it is desirable that it is 10-40 degrees C.

[0013] The collagenous fiber reproduced [was solidified and] and obtained by the spinning bath is cut

by the staple fiber in order to consider as a nonwoven sheet. If it becomes difficult to obtain the nonwoven sheet which has the intensity which resists the blood which short ** past ** and ***** between fiber decrease, and spouts in the case of ****, and cutting length causes the contamination of those other than an adaptation part that a staple fiber tends to disperse at the time of nonwoven sheet handling and it is too long Since it becomes difficult for ***** between fiber to become excessive and to obtain manufacture of uniform distributed liquid and the nonwoven sheet of uniform thickness, 1-30mm costs 1-50mm more preferably. As for cutting process which tears off or is pressed, avoiding is good, although inserting and cutting-machine-etc.-cutting is desirable and there is especially no limit in cutting process, after washing the fiber obtained by carrying out spinning, although cutting of a collagenous fiber may be performed in which stage to distribution and paper milling after spinning.

[0014] Since the form of the gel containing high-concentration salts is carried out, the collagenous fiber obtained by carrying out spinning is washed after [spinning] salts, and in order to, remove impurities other than a collagen in addition to this. When water insolubilization of the collagenous fiber is carried out by bridge formation processing in advance of removal of salts etc., it washes using the high water of the washing efficiency of salts as a cleaning agent. Moreover, when not performing bridge formation processing, since it is water-soluble, a collagenous fiber is washed using the mixed liquor of alcohols and water.

[0015] Since an isopropanol is used preferably, and the washing efficiency of salts falls as alcohols so that the ratio of alcohols is high, it is desirable to be the range which does not dissolve a collagenous fiber, and for it to be necessary to consider as the range in which washing efficiency is not reduced, and to make an alcohols ratio into 30 - 90vol%. Moreover, although washing temperature is based also on the stability of the upper shell which prevents the thermal denaturation of a collagen although the higher possible one is good from washing efficiency, and the collagen to be used, it is desirable to consider as 10-40 degrees C.

[0016] The mixed solution of the organic solvent or the organic solvent, and water which do not dissolve a collagen is distributed, and the cut collagenous fiber mills distributed liquid, and is taken as a nonwoven sheet. Although it is required to be easy to remove while not dissolving a collagen and dispersibility's being good as a dispersion medium and organic solvents, such as alcohols, ketones, and ether, are used, ethanol and an isopropanol are preferably used from the non-residual property of a solvent, and safety especially. Moreover, although it is usually common in the distributed liquid in paper milling to add a viscosity controlling agent in order to raise dispersibility, since it cannot use for the manufacture purpose of medical material, the mixed solution of the organic solvent (a debt is prevented by the swelling of fiber while raising solution viscosity) and water which added water and raised dispersibility is also used.

[0017] Moreover, rationalization of manufacture is enabled by using the dispersion medium of the same composition as the penetrant remover used for desalting washing. Although it is easy to distribute to homogeneity and the nonwoven sheet of uniform thickness and density is obtained in paper milling like a low, a low and since the collagenous-fiber concentration of distributed liquid needs a lot of distributed liquid and big equipment, considering as 0.01 - 1.00wt% is not much desirable.

[0018] By ****(ing) collagen distribution liquid equally from the lower part of ***** in paper-milling equipment, a collagen staple fiber deposits one by one to a **** screen oversize, and a uniform collagenous-fiber nonwoven sheet is formed. Although it can set up arbitrarily, the thickness of a collagenous-fiber nonwoven sheet repeats paper milling, or carries out the laminating of the nonwoven sheet, and thickness can be adjusted or it can also multilayer it.

[0019] Moreover, after it sets to this invention and paper milling mills paper in the case [paper milling], the collagenous-fiber nonwoven sheet which mixed or carried out the laminating and compounded the living body absorptivity fiber of a chitin, chitosan, an oxycellulose, a polylactic acid, a polyglycol acid, a different-species collagen, etc. can be obtained. Or the composite with living body absorptivity fiber adds living body absorptivity fiber in collagen distribution liquid in the case of paper milling, it carries out the laminating of the living body absorptivity fiber nonwoven sheet to the collagenous-fiber nonwoven sheet obtained by using together the distributed liquid of living body

absorptivity fiber etc. in living body absorptivity fiber mixture or after carrying out the laminating or milling paper, and compounds with a collagen nonwoven sheet. By composite of this living body absorptivity fiber, functions, such as antibacterial and drug release nature, were given, or the collagenous-fiber nonwoven sheet of a low cost can be obtained.

[0020] The obtained collagenous-fiber nonwoven sheet is dried by reduced pressure drying etc., and arbitrary finishing in consideration of safety required as hemostasis material, such as carrying out bridge formation processing sterilization or if needed further, and handling nature is given.

[0021]

[Example] Hereafter, an example explains this invention concretely. In addition, the performance evaluation of a collagenous-fiber nonwoven sheet depended on the method of describing below.

[0022] 1) Hemostasis nature : the adult dog which medicated the whole body with heparin 100micro/kg before the experiment start was made an incision in the abdomen under general anesthesia, and the amount of bleeding after pressing 0.1g hemostasis material for 30 seconds in the part which exfoliated only the coat of a spleen with the scalpel in the 1cmx1cm size was observed for every fixed time.

Rank A The hemostasis is the completion rank B within 1 minute. The hemostasis is the completion rank C within 3 minutes. The hemostasis is completed within 5 minutes. [0023] 2) Homogeneity (a

superintendent officer's change) : the evaluation judging of until uniform shell uneven was carried out in five stages, the higher one of homogeneity was set to five and the method of a low was set to 1.

3) Wound section contact nature : the evaluation judging of until it is inferior from fitness was carried out in five stages, the fitness was set to five and the inferior direction was set to one.

4) adhesion [between single fibers]: -- a nothing shell -- many -- the evaluation judging of until was carried out in five stages, the direction which is not was set to five, and more ones were set to one

[0024] (Example 1) The insoluble collagen obtained from fresh oxhide was processed in the pepsin of a proteolytic enzyme, and atelocollagen was obtained. 100 micrometers of apertures after dissolving in the hydrochloric-acid solution which adjusted this atelocollagen to pH 2 and considering as a temperature [of 25 degrees C], and collagen concentration 5wt% acidic solution, and a hole -- breathe out from the spinneret of a-200 number in the spinning bath which consists of sodium-sulfate 20wt% solution with a temperature of 25 degrees C It solidified and reproduced, the temperature of 25 degrees C washed the reproduction collagenous fiber with the mixed liquor of an isopropanol 80/water 20 (vol%), and the collagenous fiber was obtained.

[0025] The obtained collagenous fiber was cut, distributed liquid was prepared on condition that a-f shown in Table 1, 2.3ml in 2 and **** speed with 20 meshes [of **** meshes], and a ***** area of 300cm / after milling paper on condition that 2 5cm, reduced pressure drying was carried out and the collagenous-fiber nonwoven sheet was obtained. The performance of each obtained collagenous-fiber nonwoven sheet was shown in Table 2. Each obtained collagenous-fiber nonwoven sheet was that in which physical properties good as hemostasis material are held about them, and all have high hemostasis ability at them although a difference is seen a little by appearance, feeling, intensity, etc.

[0026] (Example 2) The insoluble collagen obtained from fresh oxhide was processed in the pepsin, and atelocollagen was obtained. 100 micrometers of apertures after dissolving in the hydrochloric-acid solution which adjusted this atelocollagen to pH 2 and considering as a temperature [of 25 degrees C], and collagen concentration 5wt% acidic solution, and a hole -- from the spinneret of a-200 number, it breathes out and reproduced in the spinning bath which consists of sodium-sulfate 20wt% solution with a temperature of 25 degrees C, the temperature of 25 degrees C washed the regenerated fiber with the mixed liquor of an isopropanol 80/water 20 (vol%), and a collagenous-fiber (b) was

[0027] On the other hand, the insoluble collagen obtained from fresh oxhide was processed in the mixed solution of a sodium sulfate, a sodium hydroxide, and monomethylamine, and atelocollagen was obtained. this atelocollagen -- the same -- carrying out -- spinning -- it washed and a collagenous-fiber (b) was obtained On condition that a which shows two sorts of obtained collagenous fibers in Table 1, after having cut, having prepared distributed liquid, milling paper and considering as a nonwoven sheet, respectively, reduced pressure drying was carried out, the laminating was carried out and the collagenous-fiber compound nonwoven multilayer-like sheet was obtained. Although the performance

of the obtained collagenous-fiber compound nonwoven sheet was shown in Table 2, the obtained collagenous-fiber compound nonwoven sheet was what has performance sufficient as **** material.

[0028] (Example 3) In the example 2, the collagenous-fiber compound nonwoven sheet was obtained like the example 2 except having replaced with a collagenous-fiber (b) and having used chitosan fiber. The performance of the obtained compound nonwoven sheet was shown in Table 2.

[0029] (Example 4) Collagenous-fiber (**) and collagenous-fiber (**) which were used in the example 2 were cut to 10mm, respectively, after having made it distribute to mixing ratio [of a two-sort staple fiber] (wt ratio) 1:1, and fiber concentration 0.1wt%, preparing distributed liquid and milling paper in an isopropanol, reduced pressure drying was carried out and the collagenous-fiber compound nonwoven sheet of the mixed state was obtained. Although the performance of the obtained collagenous-fiber compound nonwoven sheet was shown in Table 2, the obtained collagenous-fiber compound nonwoven sheet was what has sufficient performance practical as hemostasis material.

[0030] (Example 5) In the example 4, the collagenous-fiber compound nonwoven sheet was obtained like the example 4 except having replaced with a collagenous-fiber (b) and having used chitosan fiber. Although the performance of the obtained collagenous-fiber compound nonwoven sheet was shown in Table 2, the obtained collagenous-fiber compound nonwoven sheet was what has sufficient performance practical as hemostasis material.

[0031] (Example 1 of comparison) The reproduction collagenous fiber which carried out spinning and which was obtained in the example 1 was washed at the temperature of 25 degrees C by using a methanol instead of an isopropanol/water, after carrying out reduced pressure drying, cut in length of 10mm, the air blow for 10 minutes was made to distribute at the wind speed of 30 m/sec, and the collagenous-fiber curdy object was acquired. Although the performance of the acquired collagenous-fiber curdy object was shown in Table 2, since the acquired collagenous-fiber curdy object lacked in homogeneity, it needed a lot of curdy object for adhesion with the wound section. Moreover, when doubling with a wound part with a curdy object on the occasion of hemostasis disposal, a pincette could not be used, but the hand and the finger had to classify the initial complement, and not only the field of safety but operation became complicated.

[0032] (Example 2 of comparison) It flooded with the solution which added sodium chloride 15wt% glutaraldehyde 0.5%wt% at pH 4 diluted hydrochloric acid for 15 minutes, and after carrying out bridge formation processing, water fully washed the collagenous fiber obtained in the example 1. Subsequently, it cut and freeze-dried in length of 10mm, and the collagenous-fiber curdy object was acquired. Although the performance of the acquired collagenous-fiber curdy object was shown in Table 2, since fiber had hardened the acquired collagenous-fiber curdy object, flexibility was missing, and contact nature with the wound section was inferior, and hemostasis ability was also falling.

[0033] (Example 3 of comparison) After having cut the collagenous fiber obtained by carrying out bridge formation processing by the glutaraldehyde in the example 2 of comparison in length of 10mm, distributing it to fiber concentration 0.1wt% in water and milling paper, reduced pressure drying was carried out and the collagenous-fiber nonwoven sheet was obtained. Although the performance of the obtained collagenous-fiber nonwoven sheet was shown in Table 2, the obtained collagenous-fiber nonwoven sheet had the large adhesion between single fibers, and contact nature with eye rough ***** and the wound section was inferior, and hemostasis ability was also falling.

[0034] (Example 4 of comparison) When it added to water so that the collagenous fiber obtained in the example 1 might be cut in length of 10mm and it might become fiber concentration 0.1wt%, it dissolved in water and a collagenous fiber cannot mill paper.

[0035]

[Effect of the Invention] Since the collagenous-fiber nonwoven sheet by this invention demonstrates the hemostasis ability as hemostasis material enough and is excellent in the handling nature at the time of hemostasis disposal, it raises operability, and from the gestalt, to all the wound sections in a surgery field, it can be quick and it can be effectively adapted. It is very useful as hemostasis material, and according to this invention, this collagenous-fiber nonwoven sheet can be obtained simple and cheaply safely.

[Table 1]

条件	繊維長 (mm)	分散媒 (vol%)	コラーゲン繊維 濃度(vt%)
a	10	IPA100	0.1
b	40	IPA100	0.1
c	10	IPA80/水20	0.1
d	0.5	IPA100	0.1
e	120	IPA100	0.1
f	10	IPA100	3.0

* IPA:イソプロパノール

[Table 2]

	形状	不織シート 厚さ(mm)	止血性 (ランク)	均一性	創傷部 接触性	単繊維間 の接着
実施例 1 a	シート状	6	A	4~5	5	5
b	シート状	6	A	4	5	5
c	シート状	5	A	5	5	4
d	シート状	6	A~B	4	3	5
e	シート状	8	A~B	3	3	5
f	シート状	140	A~B	3	4	5
実施例 2	シート状	5	A	5	5	5
" 3	シート状	5	A	4~5	5	5
" 4	シート状	5	A~B	5	5	5
" 5	シート状	5	A~B	4~5	5	5
比較例 1	綿状	—	B	1	2	3
" 2	綿状	—	C	3	2	3
" 3	シート状	6	C	3	1	1
" 4	抄造不可	—	—	—	—	—

[Translation done.]